ANNUAL PROGRESS REPORT

SEATO Medic Study No. 3	Clinical Course and Pathologic Physiology of Thai Hemorrhagic Fever
Project No. 3A 025601 A 811	Military Medical Research Program S.E. Asia
Task 01:	Military Medical Research Program S.E. Asia
Subtask 01:	Military Medical Research Program SEASIA (Thailand)
Reporting Installation:	US Army-SEATO Medical Research Laboratory APO 146, San Francisco, California
	Division of Medical Research Laboratories
	Department of Virology
Period Covered by Report:	1 April 1963 to 31 March 1964
Principal Investigator:	Major Scott B. Halstead, MC
Associate Investigators:	Dr. Suchitra Nimmanitya*
	Captain Harvey J. Weiss
	Major Mark R. Margiotta
Reports Control Symbol:	MEDDH-288
Security Classification:	UNCLASSIFIED

* Senior Pediatrician, Children's Hospital, Bangkok

ABSTRACT

SEATO Medic Study No. 3	Clinical Course and Pathologic Physiology of Thai Hemorrhagic Fever
Project No. 3A 025601 A 811	Military Medical Research Program S.E. Asia
Task 01:	Military Medical Research Program S.E. Asia
Subtask 01:	Military Medical Research Program SEASIA(Thailand)
	Division of Medical Research Laboratories
	Department of Virology
Period Covered by Report:	1 April 1963 to 31 March 1964
Principal Investigator:	Major Scott B. Halstead, MC
Associate Investigators:	Dr. Suchitra Nimmanitya
	Captain Harvey J. Weiss
	Major Mark R. Margiotta
Reports Control Symbol:	MEDDH-288
Security Classification:	UNCLASSIFIED

The objective of this study involves clinical and laboratory examination of Thai hemorrhagic fever patients with a view to elucidate the pathogenesis of the disease. This project is concerned with the clinical and laboratory evaluation of virologically confirmed Thai hemorrhagic fever. The study consists of three parts: (1) Clinical and laboratory investigation of 82 patients at Children's Hospital (hemorrhagic fever and other diseases) conducted in August-September 1962 by Major Margiotta, (2) Hematologic evaluation of 27 dengue hemorrhagic fever patients performed by Captain Weiss in September 1962 and (3) Clinical and clinical laboratory investigation of 500 hemorrhagic fever patients conducted by Dr. Suchitra Nimmanitya, Children's Hospital. The first two parts of the study are complete except for reevaluation of virologic data and dengue virus typing. Part (3) represents a continuing study from which data is as yet incomplete.

New or important findings of this study are as follows: The diagnostic importance of fever, hepatomegaly, hemorrhagic phenomena and less frequently of shock as criteria for the diagnosis of hemorrhagic fever was stressed. Of 53 hospitalized and laboratory confirmed HF cases, 100% had a history of several days fever, 100% had hemostatic abnormality 87% had hepatomegaly and 17% were in shock. Liver disease was sufficient to produce elevated serum transaminase in 80% of patients. The respiratory tract was usually involved; 40% of children examined by X-ray had pneumonitis or pleural effusions. Capillary damage resulting in loss of plasma volume and associated electrolyte disturbances occurred commonly. Hemostatic abnormalities consisted of thrombocytopenia depression of platelet formation, prolonged prothrombin time, and prolonged silicone clotting time.

BODY OF REPORT

SEATO Medic Study No. 3	Clinical Course and Pathologic Physiology of Thai Hemorrhagic Fever
Project No. 3A 025601 A 811	Military Medical Research Program S.E. Asia
Task 01:	Military Medical Research Program S.E. Asia
Subtask 01:	Military Medical Research Program SEASIA (Thailand)
Reporting Installation:	US Army-SEATO Medical Research Laboratory APO 146, San Francisco, California
	Division of Medical Research Laboratories
	Department of Virology
Period Covered by Report:	1 April 1963 to 31 March 1964
Principal Investigator:	Major Scott B. Halstead, MC
Associate Investigators:	Dr. Suchitra Nimmanitya
	Captain Harvey J. Weiss
	Major Mark R. Margiotta
Reports Control Symbol:	MEDDH-288
Security Classification:	UNCLASSIFIED

Objectives: This study involves clinical and laboratory examination of Thai hemorrhagic fever patients with a view to elucidate the pathogenesis of the disease.

Description: The study consists of three parts: (1) Clinical and laboratory investigation of 82 hemorrhagic fever patients, and febrile and non-febrile controls undertaken at Children's Hospital, August-September, 1962 by Major M. Margiotta (2) Hematologic evaluation of 17 dengue confirmed hemorrhagic fever cases performed by Captain H. Weiss, September 1962 and (3) Clinical and clinical laboratory investigation of over 500 hemorrhagic fever patients by Dr. Suchitra Nimmanitya, Children's Hospital in 1962-1963.

Progress: Data from parts (1) and (2) are available for summary. Work on part (3) continues. The following will not be a complete description of Thai hemorrhagic fever but only a summary of new findings or findings which have been controversial.

Chief Complaint

Presenting complaint in 53 HF patients was fever (76%), headache (8.9%) cold extremities (6.6%) and malaise (4.7%).

Fever

The total duration of fever varied from 3-25 days. A 6-15 day range included 67% of patients. Fever was invariably present and was usually moderate, in the range of 101-103°F. There was no "typical" fever and in particular "saddle back" fever was not observed. The usual patient was afebrile and remained so on the 4th hospital day.

Shock

The shock syndrome characterized by hypotension, tachycardia, a weak thready pulse, cold moist skin, cool extremities, pallor, restlessness and apprehension, occurred in 9/53 hospitalized hemorrhagic fever cases. Shock was present in 7 out of 9 on admission.

Gastrointestinal Findings

Gastrointestinal tract complaints were extremely prominent and no patient failed to manifest some symptom or sign referable to the enteric tract. Abdominal pain was present in 70% of patients, abdominal tenderness in 32/58, and vomiting in 82%. Melena occurred in 7/55 HF cases, anorexia was common, diarrhea rare, while constipation was present in over 50% of patients.

Hepatomegaly, 1-3 finger breadths, was observed in 48 of 55 hemorrhagic fever cases. It was common for a patient to show striking changes in liver size over a 48-72 hour period. As shown in Table 23 mild liver chemistry derangements accompanied hepatomegaly, most predominantly serum glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenese elevations. Bilirubin levels are not commonly elevated. While there is no evidence of lowered serum albumin, the gamma globulin response is prompt and unmistakeable (Table 24).

CNS Findings

Coma or deep stupor was noted in 10 patients, in general associated with the state of peripheral collapse.

Hypoactive deep tendon reflexes were common. Seven children had pathological reflexes, usually an extensor plantar response.

Respiratory Tract Findings

Cough was observed in 42% of HF cases, but also in 47% of patients with febrile disease not etiologically related to dengue or chikungunya.

Pleural effusion was noted in 6 of 15 patients examined roentgenologically. In 1 patient the effusion was left sided; the rest were right sided.

Laboratory Findings

Polymorphonuclear leukocytosis was present in 56% of HF cases.

Serum electrolyte abnormalities frequently accompanied clinically severe disease; 23% and 22% of patients were hyponatremic or hypochloremic, respectively, The only patient with fatal outcome included in this series, a 3 year old girl, had a serum potassium of 5.9 meq/l. Electrocardiographically, she showed high peaked T waves, diffuse lowering of the R waves and deepening of the S waves in the precordial leads suggestive of hyperkalemic. Anuria, oliguria and proteninuria were rare, hematuria was not seen.

Disturbances in the hemostatic mechanism were broad. Bone marrows showed normal cellularity with suppression of megakaryocyte activity. Defects in descending order of frequency were thrombocytopenia, prolonged bleeding time, positive tourniquet test, prolonged silicone clotting time, elevated one-stage prothrombin time with reduction of factors II and V and factors VII and X and low fibrinogen. Hemostatic data is summarized in Table 25.

Summary and Conclusions: Thai hemorrhagic fever is a multiple system disease producing clinical or laboratory abnormalities in the cardiovascular system, bone marrow, liver, lungs and central nervous system. The findings which characterize this infection and serve to distinguish it from other febrile syndromes are the association of acute non-icteric hepatitis, pleural effusion and cardiovascular collapse in a febrile patient. Hemostatic abnormalities occur multiply and are related to loss of megakaryocyte function, possible sequestration of platelets, liver damage affecting the prothrombin and fibrinogen activity and other unelucidated factors responsible for abnormal clotting in siliconized tubes.

Table 23. Incidence of abnormal values in selected laboratory tests in dengue and chikungunya hemorrhagic fever, Children's Hospital, Bangkok, 1962.

Finding	Abnormal Value	Hemorrhagic Fever		Miscellaneous Febrile Disease Not Dengue or Chikungunya
		Confirmed dengue	Confirmed Chik	
Leucocytosis	10,000	32/50* (64%)	0/3	9/12 (75%)
Alk. ptase	6.75 SU/ml	0/46 (0%)	0/3	0/13 (0%)
Bilirubin	1.0 mg%	1/21 (4.8%)	0/3	0/13 (0%)
LA Peptidase	230 u	2/44 (4.5%)	0/3	1/13 (8%)
Lactic dehydrogenase	600 u	9/33 (27%)	0/3	8/13 (62%)
SGOT	50 u	37/46 (80%)	2/3 (67%)	4/13 (31%)
Hyperchloemia	115 meq/l (2 yrs.)	11/45 (24%)	2/3 (67%)	2/11 (18%)
	110 meq/l (2 yrs.)			
Hypochloremia	100 meq/l	11/46 (24%)	1/3 (33%)	1/11 (9%)
Hyperkalemia	5.6 meq/l	3/45 (6.5%)	0/3	3/12 (25%)
Hypokalemia	3.5 meq/l	17/46 (37%)	0/3	2/12 (17%)
Hyponatremia	133 meq/l	13/46 (28%)	0/3	2/12 (17%)

* No. abnormal/total tested

Table 24. Distribution of mean percent values of serum proteins during sequential stages of Thai Hemorrhagic fever in 50 patients.

Day of Disease	No. observations	% Protein determined electrophoretically				
		Gamma	Beta	Alpha 1	Alpha 2	ALB
0 - 3	10	18.3	8.0	8.2	3.5	62.1
4 - 6	25	19.2	7.3	7.9	3.3	62.3
7 - 10	34	22.5	7.4	8.5	3.8	57.8
10+	11	25.0	8.0	8.7	4.3	54.0

Table 25. Hemostatic studies in 27 dengue virus Thai hemorrhagic fever infections.

Observation	Normal value	Number abnormal/total tested	% abnormal
Platelet count	≥ 200,000	26/27	96.3
Bleeding time	≤ 7 min.	15/26	57.7
Tourniquet test	*	15/26	57.7
Silicone clotting time	≤ 45 min	13/25	52.0
One stage prothrombin	12.0-14.0 sec.	5/26	19.2
Prothrombin factor II	≥ 80%	5/26	19.2
Factor V	≥ 80%	5/26	19.2
Factor VII + X	≥ 80%	5/26	19.2
Fibrinogen	≥ 200 mg%	2/16	12.5
Glass clotting time	≤ 15 min.	0/25	0

* Graded qualitatively after inflating pressure cuff midway between systolic and diastolic for 5 min.

Publications:

1. Weiss, H.J. and Halstead, S.B.
   Studies of hemostatis in Thai hemorrhagic fever.
   I. Clinical Studies.
   Submitted to Pediatrics.

2. Weiss, H.J., Halstead, S.B. and Russ, S.B.
   Studies of hemostasis in Thai hemorrhagic fever.
   II. Hemorrhagic disease in rodents caused by chikungunya virus. To be submitted to Proc. Soc. Exp. Biol. Med.